Intensive Care Unit Management of Status Asthmaticus

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Abstract: Patients with severe asthma exacerbations, status asthmaticus (SA), or near-fatal asthma, account for almost 2 million emergency department visits annually in the United States, 497,000 hospital admissions, and 5000 deaths. Approximately, 2% to 70% (mean, 30%) of ICU admissions for asthma require mechanical ventilation, and the mortality rate of mechanically ventilated patients can range from 6% to 42% in high-risk populations. Risk stratifying patients presenting with a severe exacerbation is difficult.

In this article, the pathophysiology of near-fatal asthma and SA is reviewed. Many patients who died of SA lack the typical risk factors for death. The 2 phenotypes of severe asthma (acute and subacute onset) are similar with respect to presenting signs but their demographics and rate of decline differ after illness onset. The clinical evaluation and risk stratification of patients presenting with severe asthma exacerbations are a vital and challenging component of their care.

The rational use of inhaled and systemic therapies is also required to minimize complications and maximize benefits. Strategies for the use of mechanical ventilation that minimize the risk of barotrauma and use of permissive hypercapnia are a key to reduce mortality. The use of extrinsic positive end expiratory pressure is not contraindicated and may benefit a subset of patients. At this time, the use of noninvasive mechanical ventilation in the most severe asthma exacerbations cannot be recommended. The use of sedatives, inhalational anesthetics, and paralytics as adjuncts to mechanical ventilation have potential risks and their use must be individualized.

Key Words: status asthmaticus, near fatal asthma, mechanical ventilation, noninvasive mechanical ventilation, permissive hypercapnia, dynamic hyperinflation, barotraumas, asthma severity

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Asthma exacerbations are life threatening and the care of these patients often requires a critical care setting. The prevalence of asthma in adults is estimated at 2% to 12% and the death rates of those with asthma have been rising at the national level.[1,2] Patients with severe asthma exacerbations (status asthmaticus [SA] or near-fatal asthma) account for almost 2 million emergency department visits annually in the United States, 497,000 hospital admissions, and 5000 deaths.[3] The number of emergency department visits has doubled, and the number of hospital admissions has more than tripled in the last 20 to 25 years.[2,3] Currently, asthma accounts for between 1.7% and 2.0% of all ICU (intensive care unit) admissions.

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SA is defined as the rapid development of severe asthma symptoms that are unresponsive to usual medical therapy.[4] The attack places the patient at risk for respiratory failure. Near fatal asthma (NFA) refers to those with SA who have the most severe disease and present with hypercapnic respiratory failure in addition to metabolic acidosis. Approximately 2% to 70% (mean, 30%) of ICU admissions for asthma require mechanical ventilation, and the mortality rate of mechanically ventilated patients can range from 6% to 42% in high risk populations.[2] The clinical/historical risk factors for death from acute asthma include frequent hospitalizations, prior ICU admission, and prior intubation.[3] Less than 50% of those who die of asthma have these risk factors.[5] As a result, risk stratification in patients presenting with exacerbations is difficult.

In this article, the pathophysiology of NFA and SA is reviewed. The clinical evaluation and risk stratification of patients presenting with SA is discussed. Finally, modalities for the ICU management of these challenging patients are presented.

PATHOLOGY

Examination of the change in the airways of patients with status asthmaticus reveal the key factors involved in the pathogenesis of SA and NFA. Asthma exacerbations are characterized by airway inflammation and bronchoconstriction. The airway inflammation has several components: mucus, cellular infiltrate, airway edema, and mucosal destruction.[1,2] Smooth muscle contraction and resulting bronchoconstriction likely explain the early phases of SA. The combination of bronchoconstriction, airway inflammation, and mucus plugging are the hallmarks of a prolonged/severe attack.[3] Plugs are comprised of mucus, shed epithelial cells, eosinophils, fibrin, and other plasma proteins.[6] Plugs contribute to small airway obstruction and gas exchange abnormalities.

The cellular components of the inflammatory response include eosinophils and neutrophils. Eosinophils are present in greater numbers early in SA and their numbers tend to decrease in response to corticosteroids.[7] Neutrophils are associated with more severe exacerbations and are associated with sudden onset SA.[3,4,8,9] Neutrophil elastase enhances the secretion of glycoconjugates by glandular cells and aids in the formation of mucus plugs.[7,10] Neutrophils are also related to increased epithelial permeability and epithelial injury both of which contribute to further inflammation and plugs.

PATHOPHYSIOLOGY

Respiratory Abnormalities

The above described airway changes result in increased work of breathing (WOB). Bronchoconstriction and mucus plugging result in incomplete exhalation and increased dead space/residual volume (RV). Also, present is greater than normal airway resistance during inspiration.[6] The "trapped air" results in tidal breathing near total lung capacity (TLC) or high functional residual capacity (FRC). Patients in SA must generate extremely high inspiratory pressures to overcome the elastic recoil of the lung.[3] This can be referred to as the elastic WOB. Inspiration begins at a point where there is positive recoil pressure which is known as auto-positive end expiratory pressure (auto-PEEP) or intrinsic PEEP (iPEEP). As iPEEP progresses, the volume of trapped air increases and dynamic hyperinflation results (Fig. 1).

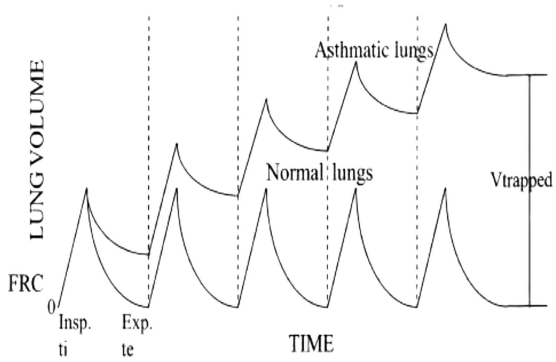

FIGURE 1. Mechanism of dynamic pulmonary hyperinflation in the setting of severe airflow obstruction. The next inspiration begins before complete exhalation of the tidal breath, leading to gas grapping and an increased end-expiratory lung volume. The pressure (in excess of atmospheric pressure) within the airways and alveoli at the end of exhalation is referred to as intrinsic or auto-PEEP. Modified from *Intensive Care Med.* with kind permission of Springer Science + Business Media.[6]

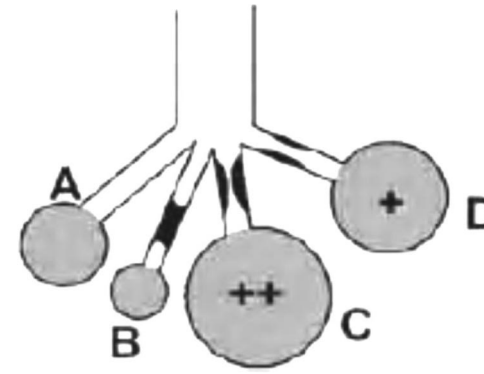

FIGURE 2. Effect of varying amounts of airway obstruction on end-expiratory alveolar volumes and pressures Modified from *Intensive Care Med.* with kind permission of Springer Science + Business Media.[11]

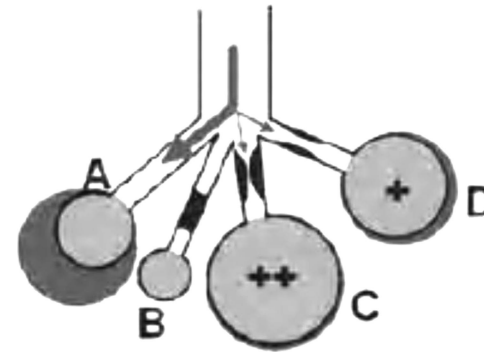

FIGURE 3. Expected distribution of V_t during positive-pressure mechanical ventilation in context of inhomogeneous obstruction. Unit A subject to expanded volumes (volutrauma). Unit B poorly ventilated and collapsed—V/Q mismatch. Unit C hyperinflated due to air trapping—subject to barotrauma. Unit D subject to barotrauma. Modified from *Intensive Care Med.* with kind permission of Springer Science + Business Media.[11]

Dynamic hyperinflation can have some beneficial effects. It may counteract atelectasis and improve gas exchange. Increased lung volumes results in increases in the caliber of airways and reduces the resistive work of breathing (WOB). This occurs at the cost of increased elastic WOB and mechanical load.[1]

In addition to the increased elastic WOB, the presence of dynamic hyperinflation results in flattening of the diaphragm and places its muscle fibers at a mechanical disadvantage. Smaller tidal volumes (V_t) are the result. The increase in dead space mentioned above causes a demand for increased minute ventilation (V_e). Also described is reduced blood flow to the diaphragm in the presence of elevated intrathoracic pressures. These changes result in respiratory muscle fatigue.

Elevated intrathoracic pressures create a phenomenon known as dynamic airways collapse (external compression of airways during exhalation), which tends to effect smaller airways. Dynamic airways collapse along with mucus plugging, airway edema, and bronchospasm creates heterogeneously ventilated lung.[11] Areas of "normal" lung exist and these areas are preferentially inflated by the delivered V_t. This has 2 major consequences: (1) worsening of V/Q mismatch as there is disproportional blood flow to well ventilated areas, and (2) increased risk of barotrauma as "normal" areas of lung are overinflated (Figs. 2, 3).[11]

Gas exchange abnormalities can vary with the duration and severity of an attack. Early stages typically present with hypocapnia. The asthmatic is able to compensate for the increase in dead space (and increased demand for V_e) initially. As the exacerbation is prolonged and fatigue ensues carbon dioxide rises and eucapnia/hypercapnia will be present. Hypoxemia is caused by ventilation perfusion (V/Q) mismatch (Figs. 2, 3) due to plugging of small airways (creating heterogeneous ventilation of small airways) and bronchospasm.[6,11] This is measured as a reduction in vital capacity.[3] In fact, most deaths in SA are felt because of occlusion of as much as 50% of the cross-sectional area of small airways 2 mm to be in diameter or less.[12]

Metabolic Acidosis

Anion-gap metabolic acidosis in SA is because of the accumulation of lactate. Lactic acidosis in SA may cause increased respiratory rate and worsening of dynamic hyperinflation. Lactic acidosis is also associated with a poor response to bronchodilators and cardiovascular collapse. Causes for lactic acidosis in SA include respiratory muscle fatigue in the setting of tissue hypoxia (resulting in anaerobic metabolism), beta-agonist use (parenteral and inhaled), and occult shock.[13,14] Investigators have observed the generation of lactate despite the use of muscle relaxants and paralytics.[13,15] In addition, these same authors found no evidence of shock or liver dysfunction. It appears that high-dose beta-agonist use is a major contributor to lactic acidosis.

One proposed mechanism for beta-agonist induced lactic acidosis is increased lipolysis with resultant increased free-fatty acids and inhibited conversion of pyruvate to acetyl-coenzyme A.[15] Inhibition of production of acetyl-coenzyme A from pyruvate results in production of lactate. Beta-receptor stimulation results in increased levels of cAMP, gluconeogenesis, and glycogenolysis. The resultant increase in plasma glucose levels provides substrate for glycolysis and lactate generation.[15] A pretreatment hyper-adrenergic state predisposes to lactic acidosis via similar mechanisms. The use of corticosteroids and theophylline enhances the sensitivity of beta-receptors to beta-agonists and amplifies the described events.[13]

Cardiovascular Abnormalities

The cardiovascular effects of dynamic hyperinflation in SA have a major impact on risk assessment, care, and outcome. Dynamic hyperinflation results in reduced venous return to the right ventricle (RV). During inspiration, because of the marked negative intrathoracic pressures that must be generated, there is rapid ventricular filling of the RV. This results in displacement of the interventricular septum into the left ventricle (LV) and a reduction in LV filling. LV systolic function is impaired not only because of reduced filling (reduction in stroke volume) but also because of increased RV and LV afterload due to the elevated intrathoracic pressures.[3]

The expected reduction in systolic blood pressure during inspiration is exaggerated, and this is known as pulsus paradoxus (PP). A difference greater than 12 mm Hg during an asthma exacerbation is significant, and a difference greater than 25 mm Hg signals a severe exacerbation.[6] In advanced SA a reduction in PP accompanies respiratory muscle fatigue (the respiratory muscles can no longer generate the inspiratory forces needed for V_t) and signals imminent respiratory arrest.

Many patients in SA present with hypovolemia due to reduced oral intake in the setting of a rapid respiratory rate and diaphoresis.[3] The reduction in venous blood return caused by elevated intrathoracic pressures may contribute to hypotension. In susceptible populations, myocardial ischemia may occur as a result of rapid HR, hypoxemia, and increased work of breathing. Arrhythmias may occur due to endogenous catechol surges, the administration of beta-agonists and theophylline.[3,16] The risk of arrhythmias is increased by coexisting hypoxemia and hypokalemia.[17]

CLINICAL FEATURES

Two phenotypes for SA/NFA exist. One can be referred to as subacute and the other sudden onset. The subacute form tends to occur in about 90% of cases, is characterized by evolution of symptoms over days to weeks, and is usually the result of poor disease control.[6,9] The sudden onset variety is characterized by acute onset of symptoms over minutes to hours. Its inciting event is often an exposure (to an irritant or allergen) or may be unknown.[6,9]

Other distinguishing features include the predominant cell type involved in the inflammatory response (Table 1). The acute form tends to respond rapidly to treatment whereas the subacute form responds more slowly to therapy. These 2 phenotypes may be difficult to distinguish initially. The ICU management of these patients is similar, but patients with acute phenotype require more timely intervention.

TABLE 1. Patterns of Respiratory Failure

	Group I Acute Severe Asthma	Group II Acute Asphyxic Asthma
Gender	Women > men	Men > women
Baseline	Moderate to severe airflow	Normal or mildly
	Obstruction	Decreased
Onset	Days to weeks	Minutes to hours
Pathology	Airway wall edema	Acute bronchospasm
	Mucus gland hypertrophy	Neutrophilic, not eosinophilic bronchitis
	Inspissated secretions	
Response to treatment	Slow	Rapid

Modified from *Intensive Care Med*.[6] with kind permission of Springer Science + Business Media.

EVALUATION

Predicting who is most likely to deteriorate or do poorly is difficult based on the historical or demographic information (Table 2). As outlined above, risk factors for death from asthma have been identified. Patients with these risk factors should be hospitalized, but many patients dying from SA do not possess these factors. The clinical assessment of an acute attack should include respiratory rate, heart rate, peak flow measurement (if possible), forced expiratory volume in 1 second (FEV1) measurement (if possible), blood pressure, documentation of PP, arterial blood gas, oxygen saturation, clinical assessment of breathing pattern (ie, abdominal paradox or use of accessory muscles), assessment of volume status, and assessment of mental status.[18] The severity of the attack can be determined using this presenting data and acute response to therapy (Table 3).

It should be noted that arterial blood gas measurements in isolation are not predictive of outcome.[3] The results must be interpreted in the clinical context. Serial measurements are more helpful than a single measurement.

The clinical assessment should also be used to search for an etiology of the asthma exacerbation. In addition, the evaluation should be used to search for complications of severe SA. These complications include pneumomediastinum, pneumothorax, pneumopericardium, subcutaneous emphysema, systemic gas emboli, subpleural cysts, tension lung cysts, bronchopleural fistula, and pulmonary interstitial emphysema. In patients undergoing mechanical ventilation, evaluation for tension pneumothorax and tracheoesophageal fistula should be a priority.[12]

Studies that should be performed in patients with severe exacerbations include chest radiograph, electrocardiogram, sputum culture, complete blood count, basic chemistries (serum glucose, blood-urea nitrogen, creatinine, liver functions tests, creatinine kinase, magnesium, calcium, serum bicarbonate, phosphate, and potassium), and serum lactate.[3] In patients with cardiac risk factors or evidence of amphetamine/cocaine ingestion, serial cardiac enzymes

TABLE 2. Risk Factors for Death From Asthma

Asthma History
Previous severe exacerbation (intubation or ICU admission)
Two or more hospitalizations in last year
Three or more emergency department visits in last year
Hospitalization or emergency department visit within past month
Greater than 2 canisters of short-acting beta agonist per month
Difficulty perceiving asthma symptoms or severity of exacerbations
Other risk factors: lack of action plan, sensitivity to alternaria
Previous severe exacerbation (intubation or ICU admission)
Social History
Low socioeconomic status
Illicit drug use
Major psychosocial problems
Inner-city residence
Comorbidities
Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease

Modified from NHLBI. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.*; Bethesda, MD: National Institutes of Health. Publication 08–4051.[18]

TABLE 3. Classifying Severity of Asthma Exacerbations

Variable	Severe Exacerbation*	Imminent Respiratory Arrest
Symptom		
Dyspnea	At rest	Unable to speak
Speech	Single words, no phrases	Lethargic, confused,
Alertness	Agitated	Obtunded
Signs		
Respiratory rate	>30/min	<10 breaths/min
Heart rate	>120/min	<60/min
Pulsus paradoxus	>25 mm Hg	Normal/low
Use of accessory muscles	Evident	Paradoxical
Wheeze	Present–loud	"Silent chest"
Functional assessment		
PEF	<40% predicted	<25% predicted
paO_2	<60 mm Hg	N/A
$paCO_2$	>42–45 mm Hg	N/A
SaO_2	<91%	N/A

*Includes acute/sudden and subacute.

Modified from NHLBI. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.*; Bethesda, MD: National Institutes of Health. Publication 08–4051.[18]

should be obtained. Patients suspected of substance abuse should have serum toxicology sent, keeping in mind that illicit drug use is a risk factor for mortality.[6]

Patients with evidence of imminent respiratory arrest/life threatening asthma should receive mechanical ventilation and be promptly admitted to an ICU (Table 3). An outcome analysis of ICU admissions in the United Kingdom by Gupta et al has identified several baseline factors/variables that are associated with mortality and the need for mechanical ventilation.[4] These indicators of the requirement for critical care remained significant after multivariate logistic regression (after adjustment for APACHE II score). The indicators of mortality in this study included high APACHE II score (>11), rapid HR (>140), hypercapnia (pCO_2 >5.7 kPa/42 mm Hg), older age (>40), and need for prehospital cardiopulmonary resuscitation. All of these factors, except older age and rapid HR, also predicted a requirement for mechanical ventilation. Other authors have found that pCO_2 greater than 63 mm Hg (±21) and a pH <7.09 (±0.12) was more common among nonsurvivors.[2] ICU admission is required for patients presenting with these characteristics whether or not mechanical ventilation is needed.

Once in the ICU, the occurrence of neurologic injury, sepsis, organ failure, and barotrauma all contribute to mortality.[4] This emphasizes the need for ongoing comprehensive ICU care in patients with SA.

PHARMACOLOGICAL THERAPIES

Inhaled Therapies

Supplemental Oxygen

Though hypoxemia is a variable characteristic of asthma exacerbations, early supportive care should always include supplemental oxygen, as patients usually have some degree of V/Q mismatch. There is some evidence that excessive use of supplemental oxygen in patients presenting with SA may result in CO_2 retention similar to that described in chronic obstructive pulmonary disease.[19] Oxygen should be delivered in a controlled fashion and guided by blood gas results.

Rarely is hypoxemia in SA refractory to moderate levels of supplemental oxygen (FIO_2 <50%). Refractory hypoxemia should not be attributed to SA alone and, if present, should be evaluated.

Beta-Agonist Therapy

The equivalent efficacy of metered-dose inhalers and nebulizer treatments has been demonstrated,[20] but most patients in the ICU setting will require nebulizer treatments because it is difficult to coordinate metered-dose inhalers use in the setting of significant dyspnea and tachypnea. There is evidence to suggest that, for a given dose of beta-agonist, response to nebulized beta-agonist therapy is greatest in NFA/SA using continuous administration.[21] One meta-analysis of nonintubated patients with SA showed equivalence of continuous delivery versus intermittent delivery.[22] In 2 of the reviewed studies, continuous delivery resulted in smaller increases in HR and less severe hypokalemia.

The risk of desaturation during delivery of continuous beta-agonist exists when air-driven nebulizers are used. In severe SA/NFA, oxygen driven nebulizers should be used. For patients who experience significant tachycardia or tremor as a side effect of albuterol therapy, the R-isomer (Levalbuterol) has equal efficacy[23] and may cause less tachycardia. It should be noted that in ventilated patients, nebulizer therapy results in elevated airway pressures. Measurements should be performed without nebulizers being delivered. Lactic acidosis induced by high-dose beta-agonist therapy was discussed above.

Anticholinergic Therapy

Anticholinergic therapy dates back 2 centuries as a therapy for respiratory disease.[21] These agents induce bronchodilation by blocking pre- and postjunctional muscarinic receptors in airway smooth muscle. Multiple studies have demonstrated that the combination of ipratropium plus a beta-agonist is superior to therapy with a beta-agonist alone.[21,24] The greatest benefit is seen in patients with the most severe obstruction. Anticholinergic therapy is also indicated in beta-blocker induced bronchospasm.[21]

Inhaled Corticosteroid Therapy

Inhaled corticosteroids are seldom used in SA, however, interest in their use is growing. One study showed the equivalence of 3000 mcg Fluticasone and 100 mg intravenous hydrocortisone in ER patients.[25] On the basis of the quick response, the mechanism of action was felt to be vasoconstriction and mucosal decongestion (Table 4). Future studies combining high-dose inhaled corticosteroids and systemic corticosteroids may show synergy or allow dose reduction of systemic medication.

TABLE 4. Vascular Effects of Corticosteroids in Airway Inflammation

	Genomic	Nongenomic
Action	Regulation of proinflammatory gene transcription	Inhibition local catechol disposal
Onset	Slow	Rapid
Targets	Angiogenesis, hyperperfusion, hyperpermeability, leukocyte recruitment	Hyerperfusion

Modified from *Proc Am Thorac Soc.*[8]

Helium-Oxygen Mixtures

Heliox in concentrations from 80:20 to 60:40 provide an inhaled gas mix with a density approximately one-third that of room air. This low density mixture reduces turbulent airflow in the airways, theoretically improving gas exchange, decreasing work of breathing, and improving delivery of nebulized medications.

Shiue and Gluck demonstrated that administration of heliox to intubated patients significantly reduced peak airway pressures and $PaCO_2$.[26] The effects of heliox in intubated patients are present only while heliox is being delivered. More sustained use in mechanically ventilated patients has not been evaluated.

Its use in mechanically ventilated patients should be reserved for those with unacceptably high airway pressures or hypercapnia[27] despite the use of aggressive bronchodilator therapy, and the appropriate use of the ventilator. The exact role of heliox in ICU patients with SA has yet to be precisely defined. Its clinical efficacy, especially in the nonintubated patient, remains a matter of debate.

Magnesium Sulfate

See subheading under "Systemic Therapies."

Systemic Therapies

Corticosteroids

As discussed, both chronic and acute asthma are characterized by inflammation, so corticosteroid therapy (oral or parenteral) is a cornerstone of acute asthma therapy, though it may take up to 24 hours for anti-inflammatory effects to reach maximum efficacy. Some improvement in lung function may be seen as soon as 4 to 9 hours after initiation, suggesting mechanisms of action other than gene regulation (Table 4).[3,7] Given the severity of disease in the ICU population, intravenous preparations are the preferred route of administration because of certainty regarding delivery.

Like beta-agonists, recommendations for optimal corticosteroid dosing are highly variable but generally range between 60 to 125 mg of intravenous methylprednisolone (or equivalent) every 6 hours.[28]

Methylxanthines

Theophylline and aminophylline, in addition to acting as bronchodilators, are anti-inflammatory and stimulate the diaphragm. Methylxanthines have largely fallen out of favor as therapies for acute asthma. In the case of severe acute asthma, however, they may still be used when other agents have failed. Meta-analyses failed to show improved outcome in patients treated with aminophylline plus beta-agonists versus beta-agonists alone.[29,30] Moreover, the use of these medications is limited by side effects and drug interactions.

Leukotriene Inhibitors

These drugs inhibit the inflammatory cascade and play an important role in the management of chronic asthma, but are less well explored in the acute setting. A multicenter, randomized, placebo-controlled trial of high-dose zafirlukast was performed in the emergency department setting and showed only a small reduction in need for admission seen in the treatment group.[31] Of note, there was no appreciable benefit with more moderate dosing. Additional studies are needed to determine whether these therapies are of benefit in the ICU setting.

Antibiotics

In the setting of acute respiratory illness, there is typically a low threshold for administration of empiric antibiotics. This is understandable given the severity with which these patients present and the current emphasis on early antibiotic administration in the setting of community acquired pneumonia and sepsis. Some suggest that occult infection with atypical organisms (*Chlamydophila* and *Mycoplasma*) may be linked to exacerbations.

The use of macrolides may lead to anti-inflammatory effects as well as antimicrobial effects.[32] Studies on this issue do not provide any conclusive evidence in favor of empiric use of macrolides in SA. There is no evidence that antibiotics improve outcome in severe acute asthma unless clear evidence of infection, such as focal infiltrate, elevated white blood count, or positive sputum culture, is present. The presence of purulent sputum may be misleading, as patients with severe acute asthma often produce purulent sputum because of significant numbers of eosinophils in respiratory secretions.[32]

Magnesium Sulfate

The use of intravenous magnesium sulfate has been controversial in SA. There have been studies both supporting and refuting the hypothesis that magnesium sulfate improves bronchodilation, either on its own or by potentiating the effects of beta-agonists. A multicenter, randomized, placebo-controlled trial of 2 mg i.v. magnesium sulfate administered to patients presenting to the emergency department with acute asthma found that only patients with very severe disease (initial FEV1 $<$25% predicted) benefited from therapy.[33] A single center randomized controlled trial of 1.2 g of i.v. magnesium sulfate failed to show benefit in adults.[34] The absence of observed benefit in the second trial may have been related to the lower dose.

As i.v. magnesium is safe and inexpensive, it is reasonable to use it as an adjunct to other standard therapies, especially in the ICU, as patients with severe obstruction stand to benefit the most. A similar conclusion can be drawn from the data concerning nebulized magnesium sulfate.[35] It is not clear, however, whether continued therapy beyond the initial dose is beneficial.

Epinephrine

Epinephrine has been given in the past as a systemic therapy for severe acute asthma (for example, 0.3–0.4 mL of 1:1000 mixture given every 20 minutes for a total of 3 doses) but must be used cautiously due to significant adverse effects. This is particularly true in elderly patients or those patients with a history of cardiovascular disease or arrhythmia.

Beta-Agonists

Terbutaline subcutaneously has been used for the management of inhaled beta-agonist refractory disease.[6] The superiority of parenteral therapy over inhaled terbutaline has been made known.[36] Intravenous albuterol is not available in the United States and comparisons with nebulized albuterol have yielded conflicting results. Isoproterenol is another option for parenteral beta-agonist therapy, but it has greater chronotropic effects than albuterol. Cardiovascular concerns regarding systemic beta-agonists are similar to those regarding the use of systemic epinephrine.

MECHANICAL VENTILATION

There are no clear cut guidelines for initiation of mechanical ventilation in SA. The large variation in the use of mechanical ventilation among ICU patients (2%–70%) reported in the literature is evidence for the lack of broadly accepted indications. Criteria for ICU admission and use of mechanical ventilation vary from region to region and institution to institution. The decision to employ mechanical ventilation is based on regional practice patterns and based, appropriately, on clinical judgment.

Those meeting criteria for imminent respiratory failure certainly require mechanical ventilation.[6] Other indications for mechanical ventilation include pH $<$7.25, $paCO_2$ $>$45 to 55, respira-

tory arrest, cardiac arrest, hemodynamic instability, and life-threatening arrythmias.[37,38] No single factor can aid the clinician in a decision to intubate a patient, but once the decision to intubate has been made there should be no delay.

Actual intubation should be performed by an experienced anesthesiologist. Intubation should be performed in a controlled and well-equipped setting. Continuous electrocardiogram, blood pressure monitoring, and pulse oximeter monitoring are vital. One should anticipate marked hypotension after intubation in a patient with SA. Acidosis, iPEEP, hypovolemia, anesthetic induced vasodilation, and loss of catecholamines all contribute to hypotension in this setting. In addition to preoxygenation, patients should be resuscitated before intubation. The use of vasopressors may also be necessary and should be readily available prior to administration of anesthetics and sedatives.

The necessary equipment to continue bronchodilator therapy should be available and compatible with the ventilator selected. The ventilator should be present and adjusted to appropriate settings prior to intubation.

Barotrauma

As discussed above, the use of mechanical ventilation carries with it the risk of barotrauma. One study showed that the mortality in any group of ventilated patients with barotrauma is 51% compared with 39% for ventilated patients without barotrauma.[39] Given the risk of barotrauma (and associated excess mortality) associated with mechanical ventilation, it should only be performed if there are strong indications.

Risk factors for barotrauma in patients ventilated for SA include elevated plateau pressures (P_{pl}), elevated iPEEP, and elevated end-inspiratory volume.[40] It is generally accepted that P_{pl} is the most useful predictor of barotrauma and dynamic hyperinflation. It is recommended that the upper limit for P_{pl} be kept below 30 to 35 cm H_2O.[11,12]

The end-inspiratory volume (V_{ei}) is also associated with dynamic hyperinflation, the risk of barotrauma, and volutrauma.[12,38] Its measurement requires the patient to be paralyzed and sedated. The exhaled volume at end inspiration is measured. Values of $V_{ei} < 20$ mL/kg are associated with reduced morbidity and mortality.[40,41] The requirement for paralysis indicate that it is not widely utilized.

The peak airway pressure or peak inspiratory pressure (PIP) is often used to monitor asthmatics on the ventilator. Several authors have indicated that PIP is not as indicative of barotrauma as P_{pl}.[11,12,38] PIP does not accurately reflect the alveolar distention.[39] In fact, the level at which the risk of barotrauma is negligible is unknown. A level of 50 cm H_2O is commonly quoted, but barotrauma has been documented at lower pressures.[12]

Even at controlled or acceptable P_{pl}, ventilator-induced lung injury may occur. In nonsedated, nonparalyzed patients inspiratory efforts may contribute to a fall in pleural pressure that contributes to transpulmonary pressure.[38] This may result in excessive V_t and overdistention of alveoli resulting in volutrauma (Figs. 2, 3) and related to the opening and closing of alveoli.

Ventilator Strategy

Goals for mechanical ventilation are to minimize barotrauma, minimize dynamic hyperinflation (and resultant cardiovascular collapse), maintain adequate oxygenation, and prevent complications of mechanical ventilation unrelated to barotrauma (ventilator associated pneumonia, deconditioning, stress ulcers, critical illness neuropathy/myopathy, and DVT/PE). Achieving the first 2 goals indicates that hypercapnia is anticipated.

There are no randomized clinical trials showing mortality benefit of a ventilator strategy that reduces dynamic hyperinflation. Observational studies have documented survival benefit.[2] Here, like the indications for starting mechanical ventilation, there are no firm guidelines for such a strategy. If volume cycled ventilation is used, variables that may be adjusted include V_t, respiratory rate (RR), expiratory time (T_{exp}), inspiratory flow (F_{in}), expiratory flow (F_{exp}), and inspiratory time (T_{in}). Combinations of these variables that result in the lowest P_{pl} and iPEEP are low V_t, low RR, and prolonged T_{exp}.[40]

Permissive Hypercapnia

Ventilator strategies that minimize barotrauma and dynamic hyperinflation are likely to result in hypercapnia. Deleterious effects of hypercapnia include a reduction in intracellular pH (if acute/severe), cerebral vasodilation (and possible increased intracranial pressure), and cardiovascular collapse.[5,38] Moderate levels of hypercapnia and resultant acidosis are generally well tolerated in patients with SA.

The reduction in intracellular pH is buffered by intracellular proteins and phosphates. There is also a reduction in proton generation and transmembrane ion exchange.[5] In the presence of adequate oxygenation, hypercapnia has a limited ability to induce significant intracellular acidosis and cell death. The intracellular adjustments to the acid challenge takes place in a matter of hours, as opposed to renal compensation for extracellular academia which takes place in hours to days.[38]

Maximum cerebral blood flow takes place at a pCO_2 of 120 mm Hg.[5] Above this level, increased intracranial pressure (ICP) can result. This may be manifested as subarachnoid hemorrhage and cerebral edema.[42] Generally, the elevated ICP results in no symptoms. The coexistence of a space occupying lesion aggravates/unmasks previous neurologic deficits. In the absence of hypoxemia or space-occupying lesion, hypercapnia induced elevation in ICP is well tolerated.[5]

Cardiovascular collapse may result from hypercapnic/acidemia induced reduction of contractility. Pulmonary hypertension (induced by acidemia/hypercapnia) may also contribute to a reduced cardiac output and the MAP may fall because of peripheral vasodilation.

Most intensivists are comfortable with a $paCO_2 < 120$ mm Hg. Various reports have described $paCO_2$ as high as 200 to 400 mm Hg (accompanied by pH <6.5) with no short-term or long-term sequelae.[5,38] In general, a pH as low as 7.2 is tolerated when employing a strategy of permissive hypercapnia. In the event that the pH is below acceptable levels, cardiovascular collapse, or neurologic changes are present, a sodium bicarbonate drip may be used.[38]

Ventilator Settings/Modes

Minimizing minute ventilation results in hypercapnia but allows for maximum expiratory time in the setting of markedly reduced expiratory flow. Prolonging expiratory time necessitates an increase in inspiratory flow (requires reduced inspiratory time) and results in increased peak inspiratory pressure which may result in proximal airway injury. It has been demonstrated that at low minute ventilation (<10 L/min), setting expiratory time greater than 4 seconds has little effect on P_{pl}. Increasing the inspiratory flow above 80 L/min (like prolonging the T_{exp}) has little impact on P_{pl} and iPEEP (if V_t and RR are set appropriately).[40] Minimizing minute ventilation by reducing V_t and/or RR is the safest and most efficient means of minimizing iPEEP and P_{pl}.

An example of initial volume cycled settings is outlined in Table 5. These recommendations apply to paralyzed (or deeply sedated) patients. An alternative to manipulating the T_{in} and T_{exp} is setting the I:E ratio $>1:2$.[43] These recommendations also call for a decelerating wave form because use of a square wave form results in higher PIP (for a given V_t, RR, T_{in} and P_{pl}). Although the PIP is less associated with barotrauma (than P_{pl}) and dynamic hyperinflation,

TABLE 5. Initial Ventilator Settings in Intubated Patients With Status Asthmaticus

Parameter	Settings
Mode	Volume-controlled ventilation
Minute ventilation	<10 L/min
Tidal volume	6–8 mL/kg ideal body weight
Respiratory rate	10–14 cycles/min
Plateau pressure	<30 cm H_2O
Inspiratory flow rate	60–80 L/min
Inspiratory flow wave form	Decelerating
Expiratory time	3.5–5 s
PEEP	0 cm H_2O
FIO_2	To an SaO_2 >90%

Modified from *Intensive Care Med.*[11] with kind permission of Springer Science + Business Media.

lower PIPs are desired. The decelerating wave form is less likely to have flow interrupted by the flow safety ("pop-off") valve.[11]

Pressure control ventilation has the advantage of setting upper limits on the P_{pl} (eg, 30–35 cm H_2O). Unfortunately, fluctuating airway resistance and iPEEP may result in variable V_t. These fluctuations may result in excessive V_t and cause volutrauma. If airway resistance drops suddenly, reventilation alkalosis may result.[11,38] Close monitoring of V_e and ABGs, in addition to adjustment of pressures to achieve V_t <6 to 8 mL/kg, can minimize these potential complications. Synchronized intermittent mandatory ventilation (SIMV) and pressure support/bi-level ventilation may also be used in less severe cases or as the patient improves.[43]

Some controversy exists about the role of extrinsic/applied PEEP (ePEEP) in the ventilated patient with SA. Tuxen[44] described an increase in P_{pl} with increasing ePEEP and reduced gas trapping at 15 cm H_20. In addition, ePEEP minimizes the pressure gradient across small airways. This reduces the effort required to trigger mechanical breaths, reduces WOB, and enhances ventilator patient synchrony.

Caramez et al[41] showed that in acute airflow obstruction (chronic obstructive pulmonary disease and asthma) varying responses to ePEEP may be observed. One response is the typical increase in P_{pl} and volumes. The second is a biphasic response with initial reduction in P_{pl} and then increase in P_{pl}. The interesting finding was called paradoxical by the investigators and revealed lowering of P_{pl} and volumes with increasing ePEEP. The ePEEP was increased as a fraction of iPEEP, V_t was set at 6 mL/kg, and RR was set at 6 to 9/min. One can attempt to apply ePEEP on an individual basis using small increments (2 cm H_2O at a time) while monitoring P_{pl}. The ePEEP should not exceed iPEEP.[43]

Inhalational Anesthetics

Inhalational anesthetics have been used in clinical scenarios where there is persistent acidosis (respiratory and metabolic), persistently elevated airway pressures, poor oxygenation, and unstable hemodynamics despite maximized conventional therapy.[45] Inhalational anesthetics have been shown to reduce expiratory resistance, reduce P_{pl}, reduce iPEEP, and hasten liberation from the ventilator. The proposed mechanism of action is the reduction in neural stimulus for bronchoconstriction and anti-inflammatory actions in alveolar cells.[46,47]

These agents have been associated with cardiovascular collapse, hepatotoxicity, nephrotoxicity, and prolonged neurologic depression. Isoflurane may not have the same toxicity as halothane. The inability of anesthesia ventilators to deliver the necessary inspiratory flows (>60 L/min) may limit their use in refractory SA.[47] Use of these ventilators in a refractory SA patient may be harmful. Some would suggest patients have the agent delivered via manual bag initially. There are modified ICU ventilators that can deliver these agents and newer anesthesia ventilators capable of achieving higher inspiratory flows. Consultation with an anesthesiologist when the use of these agents is considered is advisable.

Sedation and Paralysis

Synchrony is essential for the appropriate mechanical ventilation of patients with SA. Often deep sedation and even neuromuscular blockers are required to achieve an appropriate level of sedation that optimizes oxygenation and prevents wide variations in airway pressures. A strategy of permissive hypercapnia always requires the use of heavy sedation. Most short-acting benzodiazepines are appropriate for use in SA.

Many commonly used sedatives in the critical care setting contribute to hypotension. Ketamine is a phencyclidine that is commonly used during induction of anesthesia. It is unlikely to contribute to hypotension (inhibits reuptake of catecholamines) and has been shown to contribute to bronchodilation. The mechanism may be related to reversal of endothelin-induced bronchospasm.[48] Ketamine may be the drug of choice for rapid sequence intubation in these patients.[49]

Propofol is an intravenous hypnotic agent used for induction of anesthesia and for sedation in the ICU. It has a rapid onset of action and rapidly clears (even after prolonged use). Propofol has been shown to reduce the levels of IL-1, IL-6, IL-8 (a chemoattractant for neutrophils) and TNF-alpha. These anti-inflammatory effects may be beneficial in SA. It has bronchodilatory effects that are likely mediated by modulation of calcium influx through slow calcium channels and has been shown to reduce airway resistance in mechanically ventilated patients with SA.[50]

It should be noted that propofol has been associated with histamine release causing bronchoconstriction[51] and lactic acidosis.[52] Hypotension is a common side effect which may limit its use in a hemodynamically unstable patient. Hypertriglyceridemia and resulting pancreatitis is also a common side effect with prolonged use. The propofol infusion syndrome (metabolic acidosis, rhabdomyolysis, and cardiovascular collapse) is a rare complication that occurs with prolonged use (>72 hours) of high doses (125–200 mcg/kg/min).[50]

Neuromuscular blocking agents are used for intubation of patients with SA. Their use may also be required continuously to help achieve ventilator synchrony and prevent barotrauma. There is an independent association with myopathy (independent of steroid use) and a 30% incidence of prolonged muscle weakness when combined with high-dose corticosteroids in asthmatics.[43] Complications such as failure to wean and ventilator-associated pneumonia may result. Neuromuscular agents should be used with caution.

Noninvasive Mechanical Ventilation

Noninvasive mechanical ventilation (NIMV) or noninvasive positive pressure ventilation (NIPPV) has been used for more than 20 years in the management of SA. Contraindications to its use in SA include hemodynamic instability, mental status changes/seizures, life threatening arrhythmias, severe gas exchange abnormalities, facial abnormalities, lack of experienced staff/intensive monitoring, and excessive respiratory secretions.[36,43] The advantages of NIPPV over conventional ventilation include reduced need for sedation and lower risk of ventilator-associated complications, including nosocomial pneumonia and sinusitis. A comparison of the incidence of barotrauma between NIPPV and endotracheal intubation (ETI) was studied in a pediatric population and no difference

was noted.[53] The theoretical reduction in barotrauma has not been proven or dispelled in adults.

CPAP tends to reduce airway resistance, and resistive WOB may expand atelectasis and alleviate wide swings in intrathoracic pressure. The stabilizing of intrathoracic pressures may ameliorate the hemodynamic consequences of SA.[54] Use of bi-level NIMV results in an increase in V_t and a reduction in RR. The reduction in RR provides an increase in T_{exp} and there is also evidence for a reduction in iPEEP.[36]

Soroksky et al[55] assigned emergency room patients to bi-level NIMV (added to conventional therapy) or conventional therapy alone. The 2 groups were similar with respect to chronic illness and presenting data. Patients receiving bi-level NIMV for 3 hours demonstrated significant improvements in FEV1 and reduction in hospitalization rates compared with those receiving subtherapeutic ventilation with a sham device. Although 4 of these patients (2 in each group) had severely reduced FEV1 on presentation (<20%), none ultimately required intubation. It should be noted that none of these patients had significant hypercarbia or respiratory acidosis. A similar study performed in ICU patients with mild respiratory acidosis not immediately requiring ETI may be informative.

No randomized controlled trials of NIMV versus ETI exist. In one retrospective study by Fernandez et al,[36] patients treated with NIMV had higher pH (7.28 vs. 7.05) and lower pCO_2 (89 vs. 53 mm Hg). The investigators found no difference in length of stay (ICU or hospital), or mortality. NIMV may be added to conventional therapy in selected ICU patients (see exclusions above), but the necessary personnel required to quickly and safely intubate a patient should be readily available. NIMV should not be viewed as an alternative to ETI at this time.

MISCELLANEOUS

Extracorporeal Membrane Oxygenator

In patients with refractory severe hypoxemia, unacceptably elevated $paCO_2$ (accompanied by extreme acidemia), and barotrauma, the extracorporeal membrane oxygenator (ECMO) has been used. Case series have described the successful use of venovenous and venoarterial ECMO. Complications of ECMO included subcutaneous hematoma and intrapulmonary hemorrhage. Most patients were started on ECMO greater than 12 hours into their ICU stay, but as much as 8 days later.[46]

Bronchoscopy

Bronchoscopy can be used for the delivery of mucolytics and inspection of airways. Case reports involving pediatric patients with refractory disease and atelectasis describe the use of bronchoscopy to safely deliver rhDNase to airways obstructed by mucus plugs.[56] The dissolution of plugs resulted in improved chest x-ray and greatly improved gas exchange.

CONCLUSIONS

Severe acute asthma remains a significant source of morbidity and mortality despite advances in the treatment of chronic disease. There are numerous treatments available, both inhaled and systemic, with varying degrees of support from the literature. All of these therapies have the common goals of rapidly reversing airflow obstruction and/or treating inflammation. Though mechanical ventilation is avoided as much as possible, ventilator strategies that prolong expiratory time and reduce the risk of barotrauma have probably contributed to improved outcomes.

Much of the data on the management of SA comes from studies performed in ER patients. Therapies that have limited benefit or a barely detectable benefit in the ER (eg, leukotriene inhibitors, magnesium sulfate) may benefit ICU patients if the optimal dose, duration, and delivery can be determined. Further research in this area should improve management in this group of critically ill patients.

The prompt evaluation of severity in patients presenting with SA is critical. Identifying patients that require ICU care because of presenting condition is fairly straightforward. Identifying patients at risk for poor outcomes on the basis of historical factors is not clear. As stated earlier, only 50% of patients dying from asthma exacerbations have readily identifiable risk factors for death.[5] Research into further classification of high-risk phenotypes would be helpful. Ideally, biochemical and clinical markers are needed. Recent research has uncovered genes (chitinase-like genes) that are a marker for asthma and airway hyperresponsiveness. Variations in associated chitinase-like (CHI3L1) genes influence the risk for the development of asthma.[57] It is possible that genes (or combinations of genes) interact with chitinase-like genes and are associated with asthma severity.

Identification of genes and the molecular pathways that influence asthma severity may have several benefits. Not only one can identify biochemical/molecular markers that precisely define asthma phenotypes, but one can potentially identify high-risk phenotypes early in their hospital course. If these markers show variation with disease activity, study of asthma genes and biochemical markers could provide methods of predicting exacerbations before presentation to the ER. Results of research in this area may yield targets for novel therapies within the ICU. Alternatively, conventional therapies may be optimized by the precise recognition of phenotypes using genetics and biomarkers.

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